REMARKS

Summary of the Invention

The invention features a method of assaying a test compound for an effect on hypertension parameters by administering a test compound to a non-human mammal having a functionally variant α1 Na,K-ATPase hypertension susceptibility gene and determining whether the test compound affects hypertension parameters of the non-human mammal relative to a non-human mammal that has a wild type α1 Na,K-ATPase gene.

Summary of the Office Action

Claim 1 is pending and is rejected under 35 U.S.C. § 112, first and second paragraph. Claim 1 is also rejected under 35 U.S.C. § 103 over Medvedev et al. (J. Auton. Nerv. Sys. 72:170-176, 1998; hereinafter "Medvedev"), Vesely (U.S. Patent No. 5,691,310; hereinafter "Vesely"), or Somova et al. (Methods Find. Exp. Clin. Pharmacol. 21:412-415, 1999; hereinafter "Somova"), in combination with Herrera et al. (J. Clin. Invest. 102:1102-1111; hereinafter "Herrera"). The Examiner also objects to the priority claims in the specification, the listing of references in the specification in lieu of an information disclosure statement, and the drawings. By this reply, Applicant amends claim 1, adds new claims 2-5, and addresses each of the Examiner's objections and rejections below.

Support for the Amendments

Support for the amendment to claim 1 can be found on page 2, lines 8-10 and claim 1 as originally filed. Support for new claims 2 and 3 is found on page 4, lines 5-15. The nucleic and amino acid sequence of the wild-type α1 Na,K-ATPase gene is incorporated by reference from Shull et al. (Biochemistry 25:8125, 1987; cited in Herrera et al. Science 249:1023-1026, 1990). The nucleic and amino acid sequences of the functionally variant α1 Na,K-ATPase gene is incorporated by reference from Herrera et al. (Science 249:1023-1026, 1990). Support for new claim 4 is found on page 2, lines 8-10. Support for new claim 5 is found on page 10, line 12, through page 12, line 15. No new matter is added by the amendments.

Informalities

The Examiner states that the application lacks the necessary reference to the prior application and that the current status of the non-provisional parent application should be included. Applicant submits herewith an amendment to the priority information in the specification on page 1, lines 4-6, such that the priority information now states that the parent application (U.S.S.N. 09/653,030) of the present application is abandoned.

The Examiner also objects to the listing of references in the specification. Applicant has amended the specification to remove the list of references and will submit

an Information Disclosure Statement listing each of the references in good time. Accordingly, this objection may be withdrawn.

The Examiner requests submission of a new set of figures to overcome the draftsperson's objections detailed in form PTO 498 attached to paper no. 5. Applicant submits herewith a new set of figures in response to the draftsperson's objections. Accordingly, this objection may be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph

Claim 1 is rejected under 35 U.S.C. § 112, first paragraph, for lack of written description and lack of enablement. Each of these rejections is addressed separately below.

Written Description

Claim 1 stands rejected under 35 U.S.C. § 112, first paragraph, for an inadequate written description. Specifically, the Examiner states:

> claim 1 is readable on a genus of a non-human mammal or a transgenic non-human mammal comprising a functional variant hypertension susceptibility gene and/or a genus of a functional variant hypertension susceptibility gene...[T]he genus of a non-human mammal and/or...[the] genus of a functional variant hypertension susceptibility gene is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made.

Applicant respectfully disagrees.

The Genus of Functionally Variant α1 Na,K-ATPase Hypertension Susceptibility Genes is Adequately Described

Applicant has amended claim 1 to recite the that the genome of the non-human mammal comprises a functionally variant α1 Na,K-ATPase hypertension susceptibility gene. As is described in the specification on page 3, lines 13-20, and confirmed by the Examiner on page 3, lines 10-17, of paper no. 5, the functionally variant hypertension susceptibility gene must meet all of the following criteria: 1, identification of a functionally significant structural mutation in the relevant gene; 2, concordance of the observed genetic dysfunction with a pathophysiologic mechanism logical to the hypertension pathogenesis; 3, association of the putative hypertension susceptibility gene with hypertension in validated genetic animal models or human hypertensive patients; and 4, delineation of the mechanistic role in an *in vivo* model. These criteria, coupled with Applicant's description of a functionally variant α1 Na,K-ATPase hypertension susceptibility gene containing a Q276L mutation, can be used by one skilled in the art to identify additional functionally variant α1 Na,K-ATPase hypertension susceptibility genes that fall within the claimed genus.

The Federal Circuit held that "every species in a genus need not be described in order that a genus meet the written description requirement." *The Regents of the*

University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568 (Fed. Cir. 1997). The *Lilly* court further provides that (*Id.* at 1569; emphasis added):

> a description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus **or** of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.

Thus, the *Lilly* court does not require that Applicant reduce to practice all members of a genus, or even recite every member of the genus. Furthermore, the M.P.E.P. § 2163(II)(A)(3)(a)(ii) states that:

> "[a] representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. On the other hand, there may be situations where one species adequately supports a genus...Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed...Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces." (Citations omitted.)

Applicant has satisfied the written description requirement by providing both a representative member of the claimed genus (i.e., the functionally variant α1 Na, K-

ATPase hypertension susceptibility gene), and features common to a substantial portion of the genus (i.e., the criteria provided on page 3, lines 10-17, of the specification). These features include a biological activity that is associated with the claimed genus of functionally variant α1 Na,K-ATPase hypertension susceptibility genes (i.e., increased susceptibility to hypertension due to an altered set point for cellular Na+ metabolism with higher sodium reabsorption at unchanged Na, K-ATPase levels; see page 4, lines 20-26, of the specification). In addition to this feature, the specification teaches that other members of the claimed genus can be identified by their effect on, for example, life span, blood pressure, or renal pathology (see page 10, line 12, through page 12, line 15).

Applicant also provides the nucleic and amino acid sequence of a representative member of the genus of functionally variant α1 Na,K-ATPase hypertension susceptibility genes (see SEQ ID NO: 3 and 4, respectively, provided in the sequence listing submitted herewith). Given these sequences and the criteria described above, the skilled artisan can easily identify other homologues of this gene (e.g., the human homologue), including mutations within the protein that promote the hypertension susceptibility phenotype, using techniques widely known in the art (see, e.g., Ausubel et al., Current Protocols in Molecular Biology, John Wiley & Sons, New York, NY, (1994), and Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, N.Y., (1989)).

Accordingly, the presently claimed genus of functionally variant α1 Na,K-ATPase hypertension susceptibility genes are described not only by a recitation of a representative

member, but also by many identifying characteristics which contribute to the functional properties of the genus members. Applicant notes that either of these descriptions is sufficient to satisfy the standards articulated by the *Lilly* court and, contrary to the Examiner's assertion, a reduction to practice of all genus members is not required.

The Examiner also asserts that:

> The claimed invention as a whole is not adequately described in the specification if the claims require essential or critical elements which are not adequately described in the specification and which...[are] not conventional in the art as of applicant's effective filing date. Claiming a genus of a non-human mammal and/or a transgenic non-human mammal comprising a functional variant hypertension susceptibility gene that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement." See page 4, lines 13-20, of paper no. 5.

Applicant has amended claim 1 to recite that the method entails providing a non-human transgenic mammal whose genome comprises a functionally variant α1 Na,K-ATPase hypertension susceptibility gene. In light of this amendment, Applicant submits that all essential elements required to practice the claimed invention to the full scope are described and/or easily obtained using methods that are conventional to the art. Accordingly, this rejection should be withdrawn.

The Genus of Non-Human Mammals Comprising a Functionally Variant α1 Na,K-ATPase Hypertension Susceptibility Genes is Adequately Described

The Examiner states that:

> The as-filed specification does not provide sufficient support for the present claimed invention directed to a genus of a non-human mammal comprising a functional variant hypertension susceptibility gene and/or a genus of a hypertension susceptibility gene, except for the α1 Na,K-ATPase gene in the salt-sensitive hypertension Dahl S rat. See page 4, lines 10-13, of paper no. 5.

Applicant respectfully disagrees.

As is discussed above, the M.P.E.P. § 2163(II)(A)(3)(a)(ii) states that:

> where one species adequately supports a genus...[s]atisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed...

Applicant submits that the Dahl S rat comprising a functionally variant α1 Na,K-ATPase hypertension susceptibility gene is a representative member of the genus of non-human mammals and, as such, satisfies the written description requirement. Applicant's disclosure clearly describes both the functionally variant α1 Na,K-ATPase hypertension susceptibility gene and the use of a non-human mammal (transgenic or otherwise) comprising the gene. This description clearly places the skilled artisan in possession of the presently claimed invention. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

Enablement

The Examiner also rejects claim 1 under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner states:

> ...since the claimed invention is not supported by a sufficient description (for possessing a genus of a non-human mammal comprising a functional hypertension susceptibility gene and/or a genus of functionally variant hypertension susceptibility gene) as recited in the claims...one skilled in the art would not have known how to use and make the claimed invention so that it would operate as intended... See page 6, lines 12-17, of paper no. 5.

Applicant respectfully disagrees.

The Examiner raises three distinct issues with respect to enablement of the present invention: (i) the unpredictability of producing a transgenic animal comprising an α1 Na,K-ATPase hypertension susceptibility gene; (ii) the unpredictability of transgene expression, and (iii) the unpredictability of the resulting phenotype. Applicant will now address these issues.

Production of a Transgenic Mammal Comprising a Functionally Variant α1 Na,K-ATPase Hypertension Susceptibility Gene is Enabled

The Examiner states that the "claimed invention lies [not only] in the field of using a non-human mammal comprising a functionally variant hypertension susceptibility

gene...[, but also] in the field of using a transgenic non-human mammal comprising a heterologous functionally variant hypertension susceptibility gene." See page 7, lines 6-9, of paper no. 5. Applicant submits that, with respect to non-transgenic mammals, the presently claimed method merely requires the identification of functionally variant α1 Na, K-ATPase hypertension susceptibility genes in these mammals. As is discussed above, given the nucleic and amino acid sequence of the α1 Na, K-ATPase gene, one skilled in the art can easily use many techniques known in the art to identify other α1 Na, K-ATPase genes, including those with functional deficiencies. See, e.g., Ausubel et al., supra, and Sambrook et al., supra.

Turning to the production of a transgenic mammal comprising a functionally variant α1 Na,K-ATPase susceptibility gene, the Examiner states that:

> ...one skilled in the art would not be able to rely on the state of the art for an attempt to produce any transgenic non-human mammals other than the rat. This is because...the art of [producing] transgenic [mammals] is not predictable...with respect to transgene behavior and the resulting phenotype." See page 12, lines 7-11, of paper no. 5.

The Examiner cites Polejaeva et al. in support of the above assertion, stating that the production of transgenic animals using pro-nuclear injection was unpredictable at the time the application was filed. Contrary to this position, Polejaeva et al. describes the successful production of transgenic animals using several methods, including the injection of genetic material into the pronucleus of a zygote, the insertion of transgenes into embryonic stem cells (ES cells), and the use of somatic cell nuclear transfer.

Polejaeva et al. does indicate that one limitation of pro-nuclear injection is that DNA can only be added, not deleted or modified *in situ*. Polejaeva et al. continues by stating that gene targeting methods, in which targeted mutagenesis results in the production of transgenic animals with gene knockouts, "has been widely used for over a decade as an important tool for introducing precise modifications of the germ line." See page 120, lines 2-4 of Polejaeva et al. Therefore, Polejaeva et al. clearly does not consider the production of transgenic animals using the art-known techniques described therein as unpredictable.

In addition, the Examiner cites Rulicke et al. and Bishop in support of the statement that "prior art and post-filing art [are] replete with references which indicate that ES technology is generally limited to the mouse system at present and that only 'putative' ES cells exist for other species." See paper no. 5, lines 5-7. Although Rulicke et al. and Bishop state that ES cell technology is mainly limited to the murine system, these references clearly indicate that it has been used successfully in other systems. In addition, Rulicke et al. indicates that pro-nuclear injection has been used to produce transgenic mammals other than mice. See page 590, col. 1, lines 1-7, of Rulicke et al. Therefore, these references clearly indicate that several methods for the production of transgenic mammals were known in the art at the time of filing, and many of these methods can be used successfully to produce transgenic mammals for use in the method of claim 1. The Examiner interprets these references to suggest that the state of the art at

the time the application was filed was unpredictable with respect to the production of transgenic animals and therefore, the as-filed specification is not enabled. Contrary to this position, the court in *In re Wright* held that:

> Although not explicitly stated in section 112, to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without "undue experimentation." Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples. (999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993.))

Therefore, in light of the fact that the cited references concur that transgenic mammals can be successfully produced using one of many art-known techniques, and the fact that the specification broadly describes the use of transgenic mammals (see *In re Wright* above), Applicant submits that the enablement requirement for the production of transgenic mammals has been satisfied.

Furthermore, the Examiner, contradicting the original statement, goes on to say that:

> While the state of the art of transgenics is such that one of skill in the art <u>would be able to produce</u> [a] transgenic animal comprising a transgene of interest (e.g., hypertension susceptibility gene), it is not predictable if the transgene would be expressed at a level and specificity sufficient to be used in a method of assaying a test compound that modulates hypertension." See page 12, lines 13-16, of paper no. 5; Emphasis added.

Thus, the Examiner concedes that a person of ordinary skill in the art could make the

claimed transgenic mammals, but asserts that the resulting phenotype would be unpredictable. Applicant now addresses this issue.

Predictability of Expression

As is discussed above, the Examiner concedes that a person of ordinary skill in the art could make the claimed transgenic animals, but asserts that the resulting phenotype would be unpredictable (see page 12, lines 13-16, of paper no. 5). The Examiner continues by stating that transgene expression is dependent upon, for example, the individual gene of interest, the coding or non-coding sequences present in the trangene construct, and the specificity of transgene integration into the genome. The Examiner cites the results of Wall (Theriogenology, 1996) and Houdebine (J. Biotechnology, 1994) to support the proposition that transgene expression is unpredictable. Applicant disagrees and notes that the Examiner has improperly equated inefficiency with unpredictability.

Contrary to the Examiner's assertion, Wall demonstrates that transgene integration is very predictable, albeit inefficient. Table 1 of Wall (page 61) summarizes a number of transgenic studies from a variety of laboratories. These results indicate that transgene integration efficiency ranged from 1% in farm animals to 3% in laboratory animals. This supports Applicant's contention that the production of a wide range of transgenic mammals was, in fact, routine and predictable at the time the invention was made.

The Examiner argues further that the genetic control elements required for

appropriate expression vary from species to species. Wall discusses the "position effect" of transgene integration as influencing the ultimate expression level. For example, Wall states (paragraph bridging pages 61 and 62):

> The abbarent [sic] expression patterns (no expression or wrong expression) seen in some lines of transgenic animals has been attributed to the so-called "position effect." If a transgene lands near highly active genes, the transgene's behavior maybe influenced by endogenous genes. Other transgenes may locate in transcriptionally inactive (heterochromatin) regions. The transgene may function normally or be completely silenced by the heterochromatin. It is likely that both of these factors (position effect and unidentified control elements) contribute to lack of transgene expression in some lines and variable expression in other lines.

Wall's point is not that the artisan cannot make transgenic animals which express the transgene, but rather, that the process of doing so is inefficient; the success rate is influenced by several factors, including the location of transgene integration. Wall suggests that these factors contribute to the inherent inefficiency associated with transgenic animal production. In the context of Wall's teachings, a more thorough understanding of the essential genetic control elements will make the art more efficient, i.e. reduce the failure rate. This recognition that the field will do well to improve efficiency does not mean the technology does not work, or that it is unpredictable. In other words, Wall supports Applicant's position that transgene expression can be achieved, but that the process may be inefficient. Accordingly, all that is required to practice the claimed method is routine screening of the transgenic mammals to confirm

expression of the transgene.

The Examiner relies on Houdebine to teach that "constructs must be designed case by case without general rules to obtain good expression of a transgene (page 275, column 1, 1st paragraph)." See page 13, lines 2-5, of paper no. 5. But the passage to which the Examiner refers applies only to the use of introns in transgenic constructs. Houdebine states (page 275, first paragraph):

> The association of a given intron with the rest of the gene construct must also create cryptic signals, case by case, which modify more or less heavily the expression of the resulting transgene. Therefore, in most cases the presence of at least one intron seems to be compulsory to obtain a good expression of a transgene. However, in this respect no general rules can be edicted as long as more combination will have been obtained and examined.

As in Wall, Houdebine identifies a particular factor not at issue in the present case (i.e., the presence of intronic sequences) that possibly contributes to inefficiency in the creation of transgenic animals.

Thus, Houdebine underscores only the inherent inefficiency, but not the unpredictability, of the art of producing transgenic animals. Houdebine discusses the "unpredictable efficiency" of gene transfer, not the unpredictable expression of a successfully integrated gene (see abstract).

The test of unpredictability is not based solely on the probability of a successful outcome; even the most well understood and well controlled manufacturing processes

create defective products. In the art of transgenic animals, a practitioner may have to create many transgenic animals before arriving at one with successful transgene integration, expression, and desirable characteristics. However, neither Wall nor Houdebine suggests that making and screening for such animals is anything more than routine; indeed, each reference reports predictable success for the completion of each step. In fact, the prior art demonstrates that successful production of transgenic animals occurs with a highly predictable yield of 1-3%, depending on the species used. The art cited by the Examiner merely identifies possible factors contributing to the low efficiency of the process of producing transgenic animals, not the unpredictability of transgene expression, which requires only routine experimentation to address.

In addition, the Examiner implies that any field involving experimentation is unpredictable, and therefore, not entitled to patent protection. This is not the standard required by the statute or the case law. For example, the M.P.E.P. § 2164.01 states:

> The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation...The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. Emphasis added.

In addition, the M.P.E.P § 2164.06, citing case law, states:

> [A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). " 'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a

> reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). Emphasis added.

Since time is not a controlling factor in determining enablement (M.P.E.P § 2164.06), and the present specification provides abundant guidance for characterizing an α1 Na, K-ATPase hypertension susceptibility gene, a determination that the transgene is adequately expressed and biologically active would require only routine experimentation.

Predictability of Phenotype

The Examiner also asserts that it is highly unpredictable whether transgene expression in an animal will result in a desired phenotype. In support of this assertion, publications by Mullins et al. and Strojek and Wagner are cited. First, Applicant notes that the presently claimed method merely requires the use of a non-human mammal that comprises a functionally variant α1 Na, K-ATPase gene and the ability to determine whether any changes occur in hypertension parameters after administration of a test compound to the mammal, when compared to a non-human mammal comprising a wild-type α1 Na, K-ATPase gene. The Examiner has not provided any credible evidence showing that expression of the transgene would not occur in a transgenic mammal, or that a change in hypertension parameters would not occur after administration of a test compound to the mammal. Second, Applicant points out that the expression of an altered

phenotype in the cited art rests not on the predictability of transgenic techniques, but on the predictability of common biological activity across species. To this point, Applicant states that the α1 Na,K-ATPase gene has been identified in such divergent species as sheep (Genbank Accession No. P04074), rat (Genbank Accession No. P06685), chicken (Genbank Accession No. P09572), pig (Genbank Accession No. P19156), and human (Genbank Accession No. NP_000692). Furthermore, the biological activity of a heterologously expressed α1 Na,K-ATPase gene has also been confirmed (see Gatto et al. Am. J. Physiol. Cell Physiol. 281:C982-C992, 2001; and Sharabani-Yosef et al. J. Cell Physiol. 187:365-373, 2001; provided herewith).

The Examiner asserts that the full scope of the claimed invention is not enabled because it would require undue experimentation to identify any transgenic mammals other than the Dahl Salt Sensitive^{HSD} rat that produce the desired phenotype. Applicant points out that there is no requirement that every transgenic mammal produce the desired phenotype. A certain amount of unpredictability is permissible. The Federal Circuit, in *Atlas Powder Co. V. E.I. DuPont de Nemours & Co.*, 750 F.2d 1569, 1576, (affirming *In re Dingh-Nguyen*, 492 F.2d 856, 858 (C.C.P.A. 1974) stated:

> Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. "It is not a function of the claims to specifically exclude ... possible inoperative substances..."

Further, the Federal Circuit has stated that, "[e]nablement is not precluded by the necessity for some experimentation such as routine screening." *In re Wands*, 858 F.2d

731, 736 (Fed. Cir. 1988). The Examiner has failed to show that it would require anything more than routine screening to identify transgenic mammals which express the desired phenotype. Accordingly, for the reasons provided above, Applicant respectfully requests that the rejection of claim 1 under 35 U.S.C. § 112, first paragraph, for lack of enablement be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejects claim 1 under 35 U.S.C. § 112, second paragraph, for lack of clarity. The Examiner states that claim 1 is incomplete for omitting essential steps because the claim fails to point out what is being compared between a non-human mammal containing a variant hypertension susceptibility gene and a non-human mammal containing a wild-type hypertension gene. Claim 1 has been amended, as suggested by the Examiner, to recite the step of "determining whether the test compound affects hypertension parameters in said non-human mammal relative to hypertension parameters in a non-human mammal whose genome comprises a wild type α1 Na,K-ATPase gene." Accordingly, Applicant respectfully requests that the rejection of claim 1 under 35 U.S.C. § 112, second paragraph, be withdrawn.

Rejections under 35 U.S.C. § 103

The Examiner rejects claim 1 under 35 U.S.C. § 103 over Medvedev, Vesely, or

Somova in combination with Herrera. The Examiner states:

> At the time the invention was made it would have been prima facie obvious for a person of ordinary skill, as a matter of obvious design choice to combine the teaching of either Somova, Vesely, or Medvedev taken with Herrera to test chemical compounds in Dahl Salt-sensitive^{HSD} rats...with the α1 Na,K-ATPase gene.

Applicant respectfully disagrees.

As an initial matter, Applicant notes that the present invention claims priority to Provisional Application 60/152,011, filed September 1, 1999. Because Herrera was published less than one year before Applicant's priority date, Herrera qualifies as prior art under 35 U.S.C. § 102(a). Accordingly, Applicant directs the Examiner's attention to the Declaration of Dr. Nelson Ruiz-Opazo (under *In re Katz*), which states that Dr. Ruiz-Opazo is the sole inventor of the work described in Herrera and that the other authors worked under his direction and control, and did not contribute to the claimed inventive concepts. This Declaration is being submitted as an unsigned paper, but Applicant will send a signed Declaration in good time. Applicant submits that, based on the Declaration of Dr. Ruiz-Opazo, Herrera no longer qualifies as prior art and cannot serve as the basis for a rejection under 35 U.S.C. § 103.

The M.P.E.P. § 2143 states:

> To establish a *prima facie* case of obviousness three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available in the art, to modify the reference or to combine reference teachings. Second, there

> must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

None of Somova, Vesely, or Medvedev teaches or suggests a method of assaying a chemical compound for an effect on hypertension parameters using a non-human mammal whose genome comprises a functionally variant α1 Na,K-ATPase hypertension susceptibility gene. The Examiner acknowledges this on page 17, lines 13-16, of the Office Action (paper no. 5). Accordingly, Applicant respectfully requests that the rejection of claim 1 under 35 U.S.C. § 103 be withdrawn.

CONCLUSION

Applicant submits that the claims are now in condition for allowance, and such action is respectfully requested. Enclosed is a petition to extend the period for replying for three months, to and including January 3, 2002. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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Version with markings to show changes made

In the specification:

A marked-up version of the specification on page 1, lines 4-6, is presented below.

--This application is a continuation application and claims priority from Utility Application 09/653,030, filed September 1, 2000, now abandoned, which claims priority from Provisional Application 60/152,011, filed September 1, 1999.--

A marked-up version of the specification on page 23, line 25, through page 28, line 5 is presented below.

--As seen in Table V and Fig. 5, the most significant ANOVA results were detected at the α1 Na,K-ATPase locus (D2mgh11) and at the D2mit14 marker, 2.2 centimorgans (cM) away, for SBP (P = 0.00268), DBP (P = 0.00920), MAP (P = 0.00376). The fact that all three blood pressure measures provide similar results is in contrast to other F2 cosegregation studies that have detected cosegregation with one blood pressure parameter but not with the others, e.g., locus cosegregation with DBP and pulse pressure, but not with SBP or MAP (23). These results indicate that the α1 Na,K-ATPase locus meets criterion 4.

[References

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Other Embodiments

All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each independent publication or patent application was specifically and individually indicated to be incorporated by reference.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure come within known or customary practice within the art to which the invention pertains and may be applied to the essential features hereinbefore set forth, and follows in the scope of the appended claims.

What is claimed is:--

In the claims:

A marked-up version of claim 1 is presented below.

1. (Amended) A method of assaying a test compound for an effect on hypertension parameters, said method comprising:

(a) providing a non-human mammal whose genome comprises [with] a functionally variant α1 Na,K-ATPase hypertension susceptibility gene;

(b) administering said test compound to said non-human mammal; and

(c) determining whether said test compound affects hypertension parameters in said non-human mammal relative to hypertension parameters in a non-human mammal whose genome comprises [containing] a wild type α1 Na,K-ATPase [hypertension susceptibility] gene.